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ORIGINAL PAPER

The effect of combined phacotrabeculectomy, trabeculectomy and phacoemulsification on the corneal endothelium in the early stage: a preliminary study

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Abstract

Purpose We aimed to investigate the effect of combined phacotrabeculectomy, trabeculectomy and phacoemulsification on the corneal endothelium in the early stage.

Materials and methods In this prospective and non-randomized study, three groups were identified each consisting of 20 eyes (Group I phacotrabeculectomy, group II trabeculectomy, group III phacoemulsification). In the pre- and postop month 1, corneal endothelial cell density (CECD), coefficient of variation (CV) (polymegathism) and hexagonality (Hex) (pleomorphism) were measured by means of a non-contact specular microscope (Nidek CEM-530, NIDEK Co., Ltd. Japan).

Results The postop CECD in each of the three groups showed a significant decrease when compared with the preop period (6.1% in the phacotrabeculectomy group, 4.9% in the trabeculectomy group and 7.4% in the phacoemulsification group). The amount of decrease in the preop and postop CECD values showed no significant difference among these three groups. The postop CV value in each of the three groups showed a significant increase when compared with the preop period. The postop Hex value in each of the three groups showed no significant change when compared with the preop period.

Conclusion In our study, we observed that performing a combined phacotrabeculectomy on patients with glaucoma and cataract association in the same session did not do more harm to the corneal endothelium than other surgical methods. For this reason, this method can be applied safely to a patient population that is likely to develop corneal decompensation.

Keywords Combined phacotrabeculectomy · Trabeculectomy · Phacoemulsification · Corneal endothelial cell density · Specular microscopy

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Introduction

Co-existence of two ocular pathologies such as glaucoma and cataract leads ophthalmologists to combine surgical methods for the sake of handling both conditions simultaneously [1]. Performing trabeculectomy simultaneously with cataract surgery on patients with glaucoma not only minimizes the damage to be caused by sudden upsurges of intraocular pressure likely to occur during the early postoperative period but also provides better control of IOP compared to phacoemulsification alone [2].

The normal density of corneal endothelial cells in adults varies between 2500 and 3000 cells/mm^2 [3]. If this density drops below the threshold value, which is 400–700 cells/mm^2 [4], corneal edema develops, and the vision gets worse. Trauma or ocular surgeries lead to the death of these cells which have no divisibility capacity, hence cannot renew themselves [5]. In the wake of endothelial cell loss, the remaining cells increase their volume so as to fill the gaps caused by the dead cells, which increase and then brings about changes in their size (polymegathism) and shape (pleomorphism) [6]. Along with the development of corneal specular microscopy, it has become possible to detect corneal endothelial cell loss' "in vivo" [3].

Thus, in our study, for the purpose of preventing probable corneal complications, we aimed to investigate the effects of combined phacotrabeculectomy, trabeculectomy and phacoemulsification on the corneal endothelium and provide guidance as to which surgical method would be more reliable on a patient population with limited number of corneal endothelial cells and glaucoma associated with cataract.

Materials and methods

In this prospective and non-randomized study, 20 eyes belonging to 16 patients on whom combined phacotrabeculectomy was performed (Group I), 20 eyes belonging to 17 patients on whom trabeculectomy was performed (Group II), and 20 eyes belonging to 17 patients on whom phacoemulsification was performed (Group III) were all evaluated by the Glaucoma Unit of the Ophthalmology Clinic at Sisli Hamidiye Etfal Training and Research Hospital between October 2014 and October 2015. For this study, the approval of the Ethical Committee of Sisli Hamidiye Etfal Training and Research Hospital was received. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

The exclusion criteria involved those patients with optic disk anomaly except for glaucomatous optic disk changes, hereditary retinal diseases such as macular dystrophy and retinitis pigmentosa, retinal vascular diseases, fundus pathologies as well as pathologies that distort environmental transparency such as cataract, intravitreal opacities or corneal pathology that will hamper visual field tests and optical coherence tomography (OCT) measurements, those having difficulty in adapting themselves in the course of the study as well as those whose test reliability values have proved to be low, those with irregular astigmatism or regular astigmatism higher than 3.00 D that would affect pressure measurement, cataract density higher than grade 2 according to the Lens Opacities Classification System III (LOCS III) [7], those in whom epinephrine known to be toxic to the corneal endothelium [8] has been used for pupil dilation in cataract surgery, anterior chamber lens, sequela of infectious keratitis likely to affect the corneal endothelial parameters, inflammatory, dystrophic and degenerative corneal diseases or corneal surgical history, corneal endothelial density below 1300 cells/mm^2 and those who failed to continue their postop checkups for at least 1 month.

All operations and measurements were performed by the same surgeon. The operations were performed on all patients under general anesthesia. A limbus-based conjunctival-tenon flap and a scleral flap of 4 × 4 mm were opened for all the patients on whom trabeculectomy and phacotrabeculectomy were performed. 5-Fluorouracil (50 mg/ml)-impregnated sponges were kept under the conjunctival and scleral flaps for 2 min. Following this stage, a second transparent corneal incision at the supero-temporal area having a width of 2.75 mm was performed on those patients who received phacotrabeculectomy. Afterward, Viscoat® (sodium chondroitin sulfate 4.0% and sodium hyaluronate 3.0%), a dispersive ocular viscosurgical device (OVD), was instilled into the anterior chamber for protecting the corneal endothelium in all surgical procedures. After capsulorhexis, hydrodissection and hydrodelineation, phacoemulsification was performed (Alcon Infinity Vision System with Ozil IP (Alcon Laboratories). A foldable intraocular lens (Acrysof®,Alcon/Eyecryl Plus HSAS600, Biotech Ltd.) was placed into the capsular bag. After the excision of 3 × 1 mm of trabecular tissue, peripheral iridectomy was performed. The OVD was removed from the anterior chamber by bimanual irrigation and aspiration method. A balanced salt solution (BSS) was used for anterior chamber reformation in all surgeries. The scleral flap was sutured with 10/0 nylon. All patients were given 0.1 cc moxifloxacin (Vigamox® 0.5% ml.

Oft. Sol. Alcon) at the end of the operation to prevent the risk of endophthalmitis. In the wake of the surgery, ofloxacin (Exocin® 3 mg/mL, Allergan) was applied on all eyes every 6 h for 1 month; prednisolone-acetate (Pred forte® 1.5% ml. Oft. Sol. Allergan) was applied hourly for the first week and every 6 h in the succeeding 3 weeks on those patients who had had phacoemulsification and phacotrabeculectomy, whereas it was applied every 6 h for 1 month only on those patients who had undergone trabeculectomy; cyclopentolate (Sikloplejin® 1.5%ml Oft. Sol. Abdi İbrahim) was applied every 12 h for 2 weeks; and Tobramycin Pomade (Tobraced® 0.35% gr, Bilim Med.) was used once before bed time.

In the pre- and postop month 1, the best-corrected visual acuity (BCVA) was identified according to the Snellen Scale and was then converted into log MAR value for analysis, after which the anterior and posterior segment examination was performed. Using a non-contact tono-pachymeter (Nidek NT-530P, NIDEK Co., Ltd. Japan) by air-puff method in order to avoid fluctuations due to ocular pulsations, three automatic intraocular pressure measurements and three central corneal thickness measurements were taken for all patients. The corrected intraocular pressure values determined by the device by taking the average of these values were recorded, and the IOP readings were confirmed by Goldmann applanation tonometry (GAT). Care was taken to perform all intraocular pressure measurements at 9–10 a.m. in all patients. In the pre-and postop month 1, the measurement of the anterior chamber depth (ACD) was performed on 15 eyes from each group via a Nidek AL-Scan (NIDEK Co., Ltd. Japan) device. A non-contact specular microscope (Nidek CEM-530, NIDEK Co., Ltd. Japan) was used to take 16 automatic shots of a 0.25 × 0.55 mm central corneal endothelial surface area and make an automatic analysis of the best quality a shot performed by the device, thereby measuring corneal endothelial cell density (CECD), coefficient of variation (CV) (polymegathism), hexagonality (Hex) (pleomorphism) and central corneal thickness (CCT).

As for the statistical method, in the descriptive statistics of the data, the standard deviation, median and the lowest and highest frequency and percentage values were used. The distribution of the variables was measured through the Kolmogorov–Smirnov Test. In the analysis of the quantitative data, the Kruskal–Wallis and Mann–Whitney *U* tests were used. In the analysis of the recurrent measurements, however, the Wilcoxon test was used. In the analysis of the qualitative data, the Chi-square test was used, and when the conditions for the Chi-square test were not met, the Fisher's test was used instead. As for the analyses, SPSS 22.0 program was used.

Results

Subject characteristics are summarized in Table 1. The patients' age and gender distribution within these three groups did not show any significant difference ($p > 0.05$) (Table 1). While the BCVA significantly increased in Groups I and III, it did not show any significant difference in Group II (Table 1).

The mean anterior chamber depth (ACD) value (± SD) in Group I was determined as preop 3.1 ± 0.1 and postop 3.8 ± 0.2 mm; whereas in Group II, it was preop 3.5 ± 0.6 and postop 3.3 ± 0.6 mm; however, in Group III, mean ACD was determined as preop 3.2 ± 0.3 and postop 3.9 ± 0.3 mm (Table 2).

In Groups I and III, the postop ACD value showed a significant increase when compared with the preop period ($p < 0.05$). In Group II, the postop ACD value showed a significant decrease when compared with the preop period ($p < 0.05$) (Table 2).

The mean corneal endothelial cell density (CECD) (± SD) in Group I was determined to be preop 2326 ± 378 and postop 2184 ± 385 cells/mm^2; whereas in Group II, the mean CECD was preop 2111 ± 466 and postop 2007 ± 437 cells/mm^2; and in Group III, it was determined as preop 2516 ± 276 and postop 2329 ± 318 cells/mm^2 (Table 2). In each of the three groups, the postop CECD value showed a significant decrease when compared with the preop period ($p < 0.05$). The amount of decrease in the preop–postop CECD value did not show any significant difference among these three groups ($p > 0.05$) (Table 2).

The mean coefficient of variance (CV) (± SD) in Group I was determined to be preop 30.5 ± 6.1% and postop 34.1 ± 7.5%; whereas in Group II, it was preop 32.8 ± 11.1% and postop 35.2 ± 14.7%; and in Group III, it proved to be preop 28.9 ± 4.3% and postop 31.2 ± 4.2% (Table 2). In each of the three groups, the postop CV value showed a significant increase when compared with the preop period

Table 1 Age, Gender and pre-and post-op 1st month-BCVA among the Groups

	Group I			Group II			Group III			*P*
	Med. ± SD		Med.	Med. ± SD		Med.	Med. ± SD		Med.	
Age	66.2 ± 10.9		65.0	61.6 ± 12.1		63.5	65.8 ± 11.5		67.5	0.382
Gender										
Female	11	69%		7	41%		6	35%		0.124
Male	5	31%		10	59%		11	65%		
Visual Acuity (LogMar)										
Preop	1.03 ± 0.97		0.70	0.55 ± 0.81		0.22	0.68 ± 0.34		0.50	**0.012**
(LogMar)										
Postop	0.47 ± 0.88		0.19	0.47 ± 0.72		0.26	0.10 ± 0.12		0.04	**0.019**
Variation	− 0.56 ± 0.68		− 0.30	− 0.08 ± 0.64		0.00	− 0.58 ± 0.38		− 0.46	**0.000**
Variation *p*	**0.001**			0.937			0.000			

Kruskal–Wallis (Mann–Whitney *U* test)/Wilcoxon test

Table 2 The pre-and post-op 1st month variation among the Groups regarding the Intraocular Pressure (IOP), anterior chamber depth (ACD), corneal endothelial cell density (CECD), corneal coefficient of variation (CV), corneal endothelial hexagonality (Hex)

	Group I		Group II		Group III		*P*
	Med. ± SD	Med.	Med. ± SD	Med.	Med. ± SD	Med.	
IOP (mmHg)							
Preop	18.7 ± 7.1	16.0	20.0 ± 10.6	18.5	15.6 ± 2.9	15.5	0.176
Postop	12.6 ± 4.5	13.0	12.6 ± 5.0	12.0	13.1 ± 3.1	13.0	0.860
Variation	− 6.1 ± 8.5	− 4.0	− 7.4 ± 11.2	− 3.5	− 2.5 ± 2.6	− 1.8	0.330
Variation *p*	**0.005**		**0.001**		**0.001**		
ACD (mm)							
Preop	3.1 ± 0.1	3.1	3.5 ± 0.6	3.4	3.2 ± 0.3	3.1	**0.032**
Postop	3.8 ± 0.2	3.8	3.3 ± 0.6	3.1	3.9 ± 0.3	3.9	**0.000**
Variation	0.7 ± 0.2	0.8	− 0.2 ± 0.3	− 0.2	0.7 ± 0.3	0.7	**0.000**
Variation *p*	**0.001**		**0.008**		**0.001**		
CECD (cell/mm^2)							
Preop	2326 ± 378	2406	2111 ± 466	2155	2516 ± 276	2414	0.051
Postop	2184 ± 385	2336	2007 ± 437	1987	2329 ± 318	2302	0.103
Variation	− 142 ± 227	− 166	− 104 ± 164	− 89	− 187 ± 209	− 135	0.434
Variation *p*	**0.016**		**0.010**		**0.002**		
CV (%)							
Preop	30.5 ± 6.1	29.0	32.8 ± 11.1	29.0	28.9 ± 4.3	28.0	0.665
Postop	34.1 ± 7.5	32.5	35.2 ± 14.7	30.5	31.2 ± 4.2	30.5	0.607
Variation	3.6 ± 6.4	3.0	2.4 ± 9.7	1.0	2.3 ± 5.2	2.5	0.478
Variation *p*	**0.028**		**0.026**		**0.025**		
Hex (%)							
Preop	69.3 ± 5.4	68.5	68.4 ± 8.3	70.5	69.8 ± 6.1	70.5	0.967
Postop	65.0 ± 7.2	67.0	69.4 ± 6.4	70.5	67.6 ± 5.9	69.0	0.077
Variation	− 4.4 ± 9.2	− 4.0	1.1 ± 8.0	− 2.0	− 2.2 ± 6.3	− 3.5	0.188
Variation *p*	0.051		0.747		0.052		

Kruskal–Wallis (Mann–Whitney *u* test)/Wilcoxon test

($p < 0.05$). The amount of increase in the preop–postop CV value did not show any significant difference among these three groups ($p > 0.05$) (Table 2).

The mean hexagonality values (± SD) in Group I were determined as preop 69.3 ± 5.4% and postop 65 ± 7.2%; in group II, they were preop 68.4 ± 8.3% and postop 69.4 ± 6.4%; while in Group III, the mean Hex values were identified as preop 69.8 ± 6.1% and postop 67.6 ± 5.9% (Table 2). The postop Hex value in each of the three groups did not show any significant change when compared with the preop period ($p > 0.05$).

Discussion

The surgical method to be selected to eliminate visual loss due to the development of cataract in cases with glaucoma is still a subject under discussion. The studies have suggested that cataract extraction enables a modest long-lasting decrease in intraocular pressure in both primary open-angle glaucoma and closed-angle glaucoma patients. It is clear that this decrease will be more prominent in closed-angle glaucoma patients since the anterior chamber depth will expand after lens extraction. The studies conducted have clearly shown that lens extraction in closed-angle glaucoma causes a significant decrease in intraocular pressure [9, 10]. For this reason, lens extraction in closed-angle glaucoma has become increasingly important. On the other hand, since intraocular pressure in primary open-angle glaucoma occurs due to disruption in the trabecular meshwork structure, only cataract surgery decreases the intraocular pressure at a limited level. For this reason, filtration surgery must also be performed in addition to cataract surgery in patients with advanced glaucoma in which intraocular pressure cannot be controlled [11].

Corneal endothelium functions as a cellular pump that protects the integrity and transparency of the cornea by regulating water and ion transition between the cornea and its environment [12]. This sensitive cell layer of great significance for corneal integrity and transparency leads surgeons to seek answers as to whether surgery should be performed in a single session or in separate sessions on patients with glaucoma–cataract association.

It was important in our study to arrange the groups in similar age ranges due to the fact that corneal endothelial cell density diminishes and pleomorphism and polymegathism increase with age [13]. In our study, when the relationship between age and CECD was reviewed through Spearman's correlation, regardless of the difference among the groups, a significant negative correlation was determined between age and pre-and postop CECD. No significant correlation was determined between age and pre-and postop CECD change. Further, our study involved no significant difference among the groups in terms of age distribution.

Multivariate analyses have shown that cataract density higher than grade 2 and long phacoemulsification time strongly affect corneal endothelial cell loss. Therefore, in our study, we have excluded those patients with a cataract density higher than grade 2 according to the Lens Opacities Classification System III (LOCS III) [7]. Further, contrary to Walkow et al. [14], we did not detect any significant correlation between phacoemulsification time and corneal endothelial cell loss in groups on whom we performed phacoemulsification. (Pearson correlation (r) 0.186 and p value > 0.05).

Furthermore, various substances used in surgical procedures may also affect the corneal endothelium. In all operations performed in our study, we used Viscoat® (sodium chondroitin sulfate 4.0% and sodium hyaluronate 3.0%) as OVD, a balanced salt solution (BSS) for the aim of enabling anterior chamber formation and 0.1 cc moxifloxacin (Vigamox® 0.5% ml. Oft. Sol. Alcon) to prevent the risk of endophthalmitis. Various studies [15–18] have proven that neither has a significant toxic effect on the corneal endothelium. Further, those patients in whom intraoperative pupil dilation was required and epinephrine was used were excluded from the study due to the fact that the toxic effects of the sulfite-containing-epinephrine on the corneal endothelium have been shown [8]. In a study where Nuyts et al. [19] compared the effects of 5-FU and MMC on the corneal endothelium, it has been shown that 5-FU incubation up to 30 min has no toxic effect on the corneal endothelium. Considering that the 5-FU incubation time was 2 min in our study, we may conclude that there has been no toxic effect on the corneal endothelium.

Previous studies have suggested that anterior chamber depth increases in combined phacotrabeculectomy and phacoemulsification [20–22], while it decreases [23, 24] or remains unchanged [21] in trabeculectomy. In our study, however, the postop ACD value of the patient population who had undergone trabeculectomy (Group II) showed a significant decrease when compared with the preop period. Alvani et al. [23] pointed out an increase in the lens thickness, which is the early sign of cataractous changes, together with a decrease in the depth of the anterior chamber in patients who receive trabeculectomy. The postop ACD value of the patient population who had undergone phacotrabeculectomy (Group I) and phacoemulsification (Group III) showed a significant increase when compared with the preop period.

In our study, CECD in postop month 1 proved to be 6.1% in the phacotrabeculectomy group, 4.9% in the trabeculectomy group and 7.4% in the phacoemulsification group, and we also determined a statistically significant decrease and that the change among these three groups was insignificant. A study by Casini et al. [25] ascertained that in patients who had undergone trabeculectomy, the CECD significantly decreased by 3.5% 1 month after the surgery; and in a study conducted by Storr-Paulsen et al. [26], on the other hand, the CECD significantly decreased by 9.5% in 3 months and by 10% in 12 months; whereas in a study conducted by Lázaro García et al. [27], in which 35 patients who had undergone trabeculectomy and 21 patients who had had no surgical procedure were compared, the CECD was determined to have significantly decreased 3 months later in the group who had undergone trabeculectomy when compared with the group who had had no surgery. In a study conducted by María I. Soro-Martínez et al. where those patients who had undergone trabeculectomy only were compared to those who had undergone combined glaucoma surgery and phacoemulsification + intraocular lens implantation in one step (combined phacotrabeculectomy) or in two separate steps consisting of an initial trabeculectomy followed by phacoemulsification at a maximum interval of 3 months, the CECD was determined to have significantly decreased in each of the three groups when compared with the control group, and it was ascertained that this decrease was more prominent in the group that had undergone combined surgery performed in 2 separate sessions [6].

It is rather unclear as to why corneal endothelial density decreases in trabeculectomy, and this phenomenon is considered to be multifactorial, including medical treatment of glaucoma and preservative toxicity, contact of iris or lens with cornea due to narrow anterior chamber during or after the operation, and hypoxic damage as a result of direct pressure on corneal endothelial cells due to long-term course and high level of intraocular pressure [28, 29].

Corneal endothelial cell loss is a well-known and undesirable side effect of cataract surgery. In a study conducted by Walkow et al. which comprised 50 patients who had undergone phacoemulsification, a decrease in the corneal endothelial cell density by 8.5% was determined in the first postop year [30], whereas in a study by Ventura et al. in which 30 patients had had phacoemulsification, a significant decrease in the corneal endothelial cell density was determined at the end of the 3rd month and at the end of the 1st year [31].

Unlike other studies [22–24, 29], our study has shown a significant increase in the coefficient of variation (CV) in each of the three groups in the first postop month compared to the preop period, whereas the hexagonality value did not show any significant changes. As was the case in the study conducted by Bourne et al. [32], the fact that other cells filled the gaps caused by dead cells by expanding their fields upon corneal endothelial cell loss in the early stage may have increased the value of the coefficient of variation, which is an indicator of polymegathism.

Another point is the effect of cataract surgery performed on those patients who had formerly undergone trabeculectomy, on the functioning of the bleb and intraocular pressure. In a study conducted by İnal et al. in which 30 patients who had formerly undergone trabeculectomy and afterward had phacoemulsification were compared with 30 control patients on whom no phacoemulsification was performed, but who had formerly undergone trabeculectomy, it was observed that bleb height significantly decreased in the phacoemulsification group, yet this did not have any effect on intraocular pressure and the number of antiglaucomatous drugs used [33]. In a study by Ehrnrooth et al., it was observed that the mean intraocular pressure during the preop period was 16.2 mmHg in 46 patients who had formerly undergone trabeculectomy and afterward had phacoemulsification, whereas the number of medications used was 0.8 on average. During the postop period, however, it was observed that the mean intraocular pressure went up to 17.3 mmHg, while the number of medications used reached up to a mean number of 1.3 [34]. In a study conducted by Longo et al. which comprised two groups consisting of 108 patients each in which long-term effects of phacoemulsification in trabeculectomized eyes were compared, the need for glaucoma treatment was observed in 28.7% of the patients who had undergone phacoemulsification and in 15.7% of the patients in the control group, and it was concluded that the bleb function decreased in some eyes that had undergone a cataract surgery [35].

In those patients who have a glaucoma–cataract association, it is still a matter of discussion for ophthalmologists as to what sort of algorithm should be followed. Some authors consider that a cataract surgery should be performed in the first place and medical treatment of glaucoma should be continued thereafter, whereas some others are of the opinion that trabeculectomy should be performed first, and a cataract surgery can be performed later. Some others, on the other hand, think that a combined phacotrabeculectomy should be performed in a single session [36–38]. In our study, performing combined phacotrabeculectomy on those patients with glaucoma–cataract association in the same session provided an effective decrease in intraocular pressure while causing no more harm to the corneal endothelium than other surgical methods. Therefore, performing these two surgical interventions simultaneously on the patient population with borderline corneal endothelial cell density and likelihood of developing corneal decompensation will lead to less dysfunctioning of the bleb and provide more comfort to the patient.

Limitations

This is a preliminary study that involves a limited number of samples and a short period of 1 month for evaluating the number of corneal endothelium cells, whereas the enhancement of the number of samples and the collection of long-term data have been ongoing.

Napoli et al. [39] conducted a qualitative and quantitative evaluation of the filtering bleb by measuring the bleb wall thickness, scleral flap thickness and the reflectivity of the intrableb area by OCT (840 nm) in patients who had undergone primary trabeculectomy. Similarly, this study could have also evaluated the bleb function using the same method.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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